REMARKS

I. Status of the Claims

Claims 1-26 are pending in this application. Claims 11 and 22-26 have been withdrawn from consideration as allegedly being drawn to a nonelected invention. Claims 1-7 have been amended to correct a typographical error. Accordingly, no new matter is added by this Amendment.

II. Restriction Requirement

The Office acknowledged Applicant's election of Group I with traverse. Office Action at 2. But the Office asserts that "[b]ecause applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP §818.03(a))." *Id.* Applicant respectfully disagrees.

Applicant's response to the restriction requirement filed 23 October 2006 ("Response") specifically pointed out the reasons why the restriction requirement was improper. As noted in the Response, each of the SEQ ID NOs. 83-108 recited in the pending claims represents the sequence of a related DNA polymerase. Specifically, SEQ ID NOs. 83-108 correspond to *known* polypeptide sequences of related, Archaeal DNA polymerases. *See* Specification at pages 24-32 and Figure 7A. As explained in the Response, the wild type DNA polymerases corresponding to SEQ ID NOs. 83-108 share certain common features, including a high level of amino acid sequence homology to the Family B class of polymerases, as demonstrated by the alignment of the polypeptide sequences of certain species of the Archaeal DNA polymerase family in Figure 7B. Although the claims recite SEQ ID NOs. 83-108, they are not directed to those wild type Archaeal DNA polymerase sequences. Rather, Applicant discovered certain mutant Archaeal DNA polymerases having a mutation in a "pocket" formed by four conserved segments among

the Archaeal DNA polymerase family. Specification at page 35. These mutants possess reduced base analog (*e.g.*, uracil) detection. In a preferred embodiment, the mutant Archaeal DNA polymerase comprises a mutation at Valine 93 (V93), a conserved residue among the Archaeal DNA polymerase family. *Id*; *see also*, Figure 7B.

The specification also discloses that the V93 mutant Archaeal DNA polymerases can be further modified to include at least one mutation in the 3'-5' exonuclease domain of DNA polymerases. Specification at page 4, line 25 to page 5, line 24; page 35, lines 12-16. The exonuclease domain is conserved among DNA polymerases and comprises three conserved motifs (exo I, exo II, and exo III), which are well known to those of skill in the art. Specification at page 32; *see also* Figure 7B (showing alignment of conserved exo I, II, and III motifs in several species of Archaeal DNA polymerases). As appreciated in the art, mutations in the DNA polymerase exonuclease domain result in mutant polymerases having deficient 3'-5' exonuclease activity.

Applicant has shown that the V93 residue is conserved among the Archaeal DNA polymerase family. Furthermore, it is known in the art that DNA polymerases contain three conserved motifs in the 3'-5' exonuclease domain. *See* Specification at 32; Figure 7B. Accordingly, to cover the proper scope of their invention, claims 1-7 are generic claims directed to mutant versions of Archaeal DNA polymerases (SEQ ID NOs. 83-108) comprising a mutation at V93 and at least one mutation in the conserved exo I, exo II, and/or exo III motifs.

By requiring Applicant to elect a single species of mutant DNA polymerase the Office has improperly limited the scope of the claims through its requirement for restriction. Specifically, in issuing the restriction requirement, the Office has, without Applicant's permission or approval, limited the scope of the pending claims to a specific species disclosed in

the specification (mutant versions of SEQ ID NO:89). Applicant respectfully submits that it has a statutory right under 35 U.S.C. § 112, second paragraph, to claim the subject matter it regards as their invention as it chooses. Issuing a restriction requirement by incorporating an unclaimed limitation in an effort to limit the claim to disclosed embodiments, with the idea that Applicant would have to carve up that claim and pursue the non-elected subject matter in separate applications, violates this right under § 112. Indeed, the C.C.P.A. has characterized such action as tantamount to a refusal to examine. *See In re Weber*, 198 U.S.P.Q. 328 (C.C.P.A. 1978); *In re Haas*, 198 USPQ 334 (C.C.P.A. 1978).

In view of the above remarks, Applicant requests the Office to reconsider and withdraw the restriction requirement as to each of the mutant Archaeal DNA polymerases covered by the pending claims. In the event that the Office does not withdraw the restriction requirement, Applicant reserves the right to Petition the Commissioner to withdraw the restriction requirement, and/or to prosecute the non-elected claims in divisional or continuation applications.

III. Claim Objections

The Office objects to claims 1-7 for reciting "at lease one amino acid mutation . . ." instead of "at least one amino acid mutation." Applicant has amended claims 1-7 to recite "at least one amino acid mutation" and respectfully requests that the Office withdraw this objection.

IV. Rejections Under 35 U.S.C. §112, First Paragraph

A. The Specification Provides Written Description Support for the Pending Claims

The Office rejects claims 1-10 and 12-21 under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter that is not described in the specification so as to reasonably convey to the person skilled in the art that Applicant was in possession of the claimed invention

at the time the application was filed. Office Action at 3. Applicant respectfully traverses this rejection.

Claim 1 is directed to an Archaeal DNA polymerase comprising an amino acid sequence selected from SEQ ID NOs. 83-108 and further comprising:

1) at least one amino acid mutation in exo I motif, and

2) an amino acid mutation at V93, wherein said Archael DNA polymerase is deficient in 3'-5' exonuclease activity. Claims 2-7 are similarly directed to Archael DNA polymerases with an amino acid mutation at V93 and deficient 3'-5' exonuclease activity but further recite at least one amino acid mutation in exo II motif (claim 2), exo III motif (claim 3), each of exo I and exo III motifs (claim 4), each of exo II and exo III motifs (claim 5), each of exo I and exo II motifs (claim 6), and each of exo I, exo II, and exo III (claims 7).

According to the Office, "[t]he specification . . . only provides those Archaeal DNA polymerases wherein said mutant DNA polymerase has the amino acid sequence of SEQ ID NO:89 with a single mutation at position 93 . . . wherein said DNA polymerase is deficient in 3'-5' exonuclease activity. That is not true.

The specification discloses several mutant DNA polymerases having different mutations at V93. *See e.g.*, Specification at page 36, lines 7-17. It also provides several working examples using different Archaeal DNA polymerases. Specification, page 76, line 6 to page 77, line 16. In addition, the specification teaches in detail how to make other mutant DNA polymerases. Specification at pages 41-44. Given this guidance, one of skill in the art would be able to generate other mutant Archael DNA polymerases with a mutation at V93.

Furthermore, the specification discloses that the V93 mutant Archaeal DNA polymerases can be further modified to include at least one mutation in the 3'-5' exonuclease domain of DNA

polymerases. Specification at page 4, line 25 to page 5, line 24; page 35, lines 12-16. The exonuclease domain is conserved among DNA polymerases and comprises three conserved motifs (exo I, exo II, and exo III), which are well known to those of skill in the art. Specification at 32. Figure 7B further exemplifies the conserved structure of these three exonuclease domains in several species of Archaeal DNA polymerases. In the species disclosed in Figure 7B, the exo I motif corresponds to amino acids 141-143, the exo II motif corresponds to amino acids 210-215, and the exo III motif corresponds to amino acids 311-315. As appreciated in the art, mutations in the DNA polymerase exonuclease domain result in mutant polypeptides having deficient 3'-5' exonuclease activity. *See e.g.*, Specification at page 32. The specification provides specific examples of mutant Archaeal DNA polymerases with deficient 3'-5' exonuclease activity, including those with a mutation at the position corresponding to D141 and/or E143. Specification at page 33. Applicant also combined the exonculease mutants with the V93 mutants to produce mutant Archaeal DNA polymerases with deficient 3'-5' activity. Specification at page 78, lines 10-11; Figures 15-16. As noted above, the specification teaches in detail how to generate other mutants with at least one mutation in the exo I, exo II, and/or exo III domains. Specification at pages 41-44. It also teaches routine methods to screen mutants for deficient 3'-5' activity. Specification at 33-34 and 48-51. Accordingly, the specification discloses more than "a single mutation at position V93," as asserted by the Office.

The written description requirement of 35 U.S.C. § 112, first paragraph, does not require a description of the complete structure of every species within a chemical genus. *Utter v. Hiraga*, 845 F.2d 993, 998, 6 USPQ2d 1709, 1714 (Fed. Cir. 1988) ("A specification may, within the meaning of 35 U.S.C. § 112, ¶ 1, contain a written description of a broadly claimed invention without describing all species the claim encompasses.")

The Court of Appeals for the Federal Circuit has addressed the issue of what constitutes adequate written description in an analogous situation for a claim drawn to a nucleic acid. In *Enzo Biochem, Inc. v. Gen-Probe Inc.*, 323 F.3d 956, 964, 63 USPQ2d 1602 (Fed. Cir. 2002), the court adopted a portion of the PTO's Guidelines stating that:

> the written description requirement can be met by "show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics . . . *i.e.*, complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of characteristics."

This is precisely what Applicant has done.

The Office further asserts that "[t]here is no disclosure of any particular structure to function/activity relationship in the disclosed species that would put one in possession of the genus of all possible mutant archaeal DNA polymerases that are deficient in the 3'-5' exonuclease." Applicant disagrees.

As noted above, there was a known correlation in the art between the conserved exonuclease domain of DNA polymerases and 3'-5' exonuclease activity. Specification at page 32. Thus, it was appreciated in the art that mutations in the conserved DNA polymerase exonuclease domain (exo I, exo II, or exo III motifs) result in mutant polypeptides having deficient 3'-5' exonuclease activity, as recited in the pending claims. *See e.g.*, Specification at page 32. Furthermore, the specification provides additional examples of mutations in the exonuclease domain resulting in deficient 3'-5' exonuclease activity. Specification at page 33 and 75. The rejected claims recite that the Archaeal DNA polymerase comprises at least one mutation in the exo I, exo II, or exo III domains (or combinations thereof). Accordingly, given the known and disclosed correlation between the conserved, DNA polymerase exonucelase domain (structure) and its 3'-5' exonuclease activity (function), Applicant has adequately

described the claimed subject matter. For these reasons, Applicant requests that the Office reconsider and withdraw this written description rejection.

B. Claims 1-10 and 12-21 are Enabled

The Office rejects claims 1-10 and 12-21 under 35 U.S.C. §112, first paragraph, alleging that the specification does not enable one of skill in the art to make and use the invention commensurate in scope with the claimed invention. Office Action at 5. Specifically, the Office asserts that

> [t]he specification does not support the broad scope of the claims which encompasses all modifications and fragments of any mutant Archaeal DNA polymerase comprising the amino acid sequence of SEQ ID NO:89 and comprising at least one mutation in an exo motif and another at position V93, that is deficient in 3'-5' exonuclease activity because the specification does not establish: (A) regions of the protein structure which may be modified without effecting [*sic*, affecting] 3'-5' exonuclease activity; (B) the general tolerance of Archaeal DNA polymerase to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any amino acid residue of any Archaeal DNA polymerase with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Id. at 6-7. Applicant respectfully traverses this rejection.

The specification, coupled with the knowledge in the art, provides substantial guidance as to the specific, conserved motifs within Archaeal DNA polymerases that are associated with the 3'-5' exonuclease activity of the polymerases. As explained in the specification:

> The 3'-5' exonuclease activity associated with proofreading DNA polymerases can be reduced or abolished by mutagenesis. Sequence comparisons have identified three conserved domains (exo I (DXE), II (NX_{2-3}(F/Y)D), III (YX_3D) in the 3'-5' exonuclease domain of DNA polymerases (reviewed V. Derbyshire, J.K. Pinsonneault, and C.M. Joyce, Methods Enzymol. 262, 363 (1995)).

Specification at page 32. Thus, contrary to the Office's assertions, the specification establishes that it was known in the art that specific, conserved domains are associated with 3'-5'

exonuclease activity in DNA polymerases and that mutations in those domains result in diminished 3'-5' exonuclease activity. Moreover, given the known correlation between structure (the conserved exo I, II, and III motifs) and function (3'-5 exonuclease activity), the specification provides a rational and predictable scheme for modifying amino acids in the conserved exo I, exo II, and/or exo III motifs of an Archaeal DNA polymerase to generate mutant DNA polymerases having deficient 3'-5' exonuclease activity, as recited in the claims.

Other *Wands* factors also weigh in favor of enablement. At the time the application was filed, the level of skill in the relevant art was high. As discussed above, the specification discloses several working examples—species having a mutation at V93 and at least one mutation in the exo I, exo II, or exo III motif where the mutant DNA polymerase is deficient in 3'-5' exonuclease activity. Moreover, methods of making mutant DNA polymerases and screening for 3'-5' exonuclease activity were known in the art and described in the specification. *See* Specification at 33 and 41-51. One of skill in the art could routinely make mutations at V93 and one or more of the exo I, exo II, or exo III motifs of a DNA polymerase and screen those mutant polymerases to determine which ones have deficient 3'-5' exonuclease activity. Thus, the experimentation involved to produce other mutant DNA polymerases falling within the scope of the claims, and thus practice the full scope of the pending claims, would have been routine and well within the skill of those in the art. *See e.g.*, *Johns Hopkins Univ. v. Cellpro, Inc.*, 152 F.3d 1342, 1360, 47 USPQ2d 1705, 1719 (fed. Cir. 1989 ("test [for undue experimentation] is not merely quantitative . . . if it is merely routine."). A "patent need not teach, and preferably omits, what is well known in the art." *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986). Accordingly, for these reasons, Applicant respectfully

requests that the Office reconsider and withdraw this enablement rejection of claims 1-10 and 12-21.

IV. Double Patenting Rejections

The Office provisionally rejects claims 1-10 and 12-21 on the grounds of nonstatutory obviousness-type double patenting as allegedly unpatentable over claims 1, 3-5, 13, 15, 17-29, 31-42, 58-66 of copending Application No. 10/298,680. Office Action at 8. Applicant requests that the Office hold this provisional rejection in abeyance until one of the two patent applications in question is deemed to be in condition for allowance. At that time, if the Office still believes that the claims conflict with each other, Applicant will take the appropriate action to address the possibility of double patenting. *See* M.P.E.P. §804.

V. Conclusion

In view of the foregoing Amendment and Remarks, Applicant submits that this application is in condition for allowance. Applicant therefore requests entry of this Amendment, the Examiner's reconsideration and reexamination of the application, and the timely allowance of the pending claims.

Applicant believes that no fees or petitions are required for entry of this paper. However, if any petitions are required, please grant them, and if any fees are due, please charge them to Deposit Account No. 50-3740.

Respectfully submitted,
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